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Comparison of Outcomes after Device Closure and Medication Alone in Patients with Patent Foramen Ovale and Cryptogenic Stroke in Korean Population

Jeonggeun Moon[1], Woong Chol Kang[1], Sihoon Kim[1], Pyung Chun Oh[1], Yae Min Park[1], Wook-Jin Chung[1], Deok Young Choi[2], Ji Yeon Lee[3], Yeong-Bae Lee[4], Hee Young Hwang[5], and Taehoon Ahn[3]

[1]Cardiology, Departments of Internal Medicine, [2]Pediatrics, [3]Anesthesiology, [4]Neurology, and [5]Radiology, Gachon University, Gil Medical Center, Incheon, Korea.

Purpose: To compare the effectiveness of device closure and medical therapy in prevention of recurrent embolic event in the Korean population with cryptogenic stroke and patent foramen ovale (PFO).

Materials and Methods: Consecutive 164 patients (men: 126 patients, mean age: 48.1 years, closure group: 72 patients, medical group: 92 patients) were enrolled. The primary end point was a composite of death, stroke, transient ischemic attack (TIA), or peripheral embolism.

Results: Baseline characteristics were similar in the two groups, except age, which was higher in the medical group (45.3±9.8 vs. 50.2±6.1, $p<0.0001$), and risk of paradoxical embolism score, which was higher in the closure group (6.2±1.6 vs. 5.7±1.3, $p=0.026$). On echocardiography, large right-to-left shunt (81.9% vs. 63.0%, $p=0.009$) and shunt at rest/septal hypermobility (61.1% vs. 23.9%, $p<0.0001$) were more common in the closure group. The device was successfully implanted in 71 (98.6%) patients. The primary end point occurred in 2 patients (2 TIA, 2.8%) in the closure group and in 2 (1 death, 1 stroke, 2.2%) in the medical group. Event-free survival rate did not differ between the two groups.

Conclusion: Compared to medical therapy, device closure of PFO in patients with cryptogenic stroke did not show difference in reduction of recurrent embolic events in the real world's setting. However, considering high risk of echocardiographic findings in the closure group, further investigation of the role of PFO closure in the Asian population is needed.

Key Words: Patent foramen ovale, device closure, ischemic strokes, transient ischemic attack

INTRODUCTION

Patent foramen ovale (PFO) has been recognized as a possible cause of ischemic stroke or transient ischemic attack (TIA).[1] Recently published randomized controlled trials comparing PFO closure versus medical therapy have shown no difference in the risk of recurrent stroke or TIA between the two groups,[2-4] However, meta-analyses, including non-randomized data or focusing on trials which used the Amplatzer closure device, indicate an evidence of a benefit of PFO closure.[5,6] PFO closure appears to be a very appealing concept, potentially avoiding the need for long-term anti-platelet or anticoagulation therapy. However, there is a paucity of data regarding efficacy and safety of PFO closure for prevention of stroke or TIA in Asian populations who are more prone to bleeding as a result of blood thinning therapy.[7] This study represents our experience with the Amplatzer PFO Occluder (St. Jude Medical, St. Paul, MN, USA) in Korean patients with PFO and history of prior cryptogenic ischemic stroke or TIA.

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Corresponding author: Dr. Woong Chol Kang, Cardiology, Department of Internal Medicine, Gachon University, Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea.
Tel: 82-32-460-3054, Fax: 82-32-469-1906, E-mail: kangwch@gilhospital.com

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MATERIALS AND METHODS

Study population

This study is a prospective observational study from the Gil Medical Center PFO registry. From October 2010 to August 2014, 184 consecutive patients with stroke/recurrent TIA and PFO documented on transesophageal echocardiography (TEE) and no other identifiable cause of the ischemic event, such as no carotid or intracranial artery stenosis, no atrial fibrillation and no thrombus or atheromatous plaque at aortic arch, were analyzed. Of these patients, those who were aged 18–60 and underwent a PFO closure or medical therapy alone were enrolled in this study. PFO closure was determined according to Heart team's discretion (consist of cardiologist, neurologist and radiologist) based on patient's clinical data, echocardiographic findings and patient's preference. Fifteen patients were excluded due to their age, and 5 patients were lost during the follow-up period (Fig. 1). Finally, 164 patients (men: 126 patients, mean age: 48.1±8.5 years) were eligible for this study. The closure group included 72 patients and 92 patients were included in the medical group (medical therapy only). This study was approved by the Institutional Review Board of the Gil Medical Center.

PFO closure procedures

The closure procedure was performed under general anesthesia. After femoral venous access, the PFO was crossed with a 5 Fr multipurpose catheter. The multipurpose catheter was advanced into the left upper pulmonary vein and exchanged over a 0.035 inch J-tipped stiff guidewire for an 8 Fr or 9 Fr guiding sheath. Procedural anticoagulation was initiated with 5000 unit intravenous heparin. The appropriate device size was selected based on TEE measurements of the distance between the PFO and the aortic root. Once selected, the device was advanced through the sheath to the tip and, subsequently, the sheath and device were pulled back as a unit from the left upper pulmonary vein into the left atrium. While maintaining the position of the device, the sheath was gently pulled back allowing deployment of the left atrial disk. Under TEE guidance, the expanded left atrial disk was then retracted together with the sheath to the atrial septum, and, following verification of septal abutment, the sheath was pulled back, further allowing deployment of the right atrial disk. Upon confirmation of successful positioning by both TEE and fluoroscopy, the device was released. Recommended antiplatelet therapy following the procedure included aspirin 100 mg daily and clopidogrel 75 mg daily for at least 3 months. Follow-up transthoracic echocardiography (TTE) or TEE with agitated saline test was performed between 1 and 3 months after the procedure. Procedural success was defined as successful implantation of device without any procedure-related complication and in-hospital mortality or morbidity.

In the medical group, antithrombotic therapy was left to the discretion of the treating physician and could have included anti-platelet therapy or oral anticoagulation.

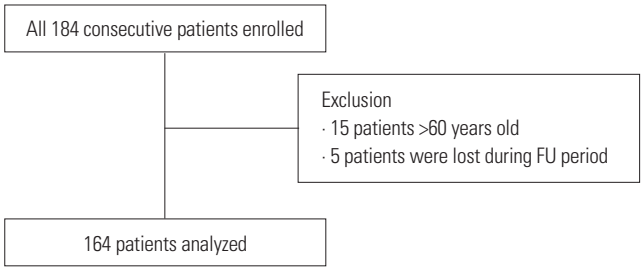

Fig. 1. Diagram for detailed enrollment of patients.

Echocardiographic variables

Septal hypermobility refers to interatrial septal excursion during the cardiac cycle of 10 mm or more from the midline. Shunt refers to agitated saline contrast (bubbles) appearing in the left atrium within 3 cardiac cycles of right atrial opacification. The degree of shunting was defined as small if 3–9 contrast bubbles appeared, moderate if 10–30 contrast bubbles appeared, and large if more than 30 contrast bubbles appeared in the left atrium.[8]

Definitions and study end points

Definition of risk of paradoxical embolism (RoPE) score was based on the previously published data.[9] The primary end point was a composite of death, ischemic stroke, TIA, or peripheral embolism. Secondary end points were individual components of the primary end point as well as cardiovascular death, new-onset atrial fibrillation, myocardial infarction (MI), hospitalization related to the PFO or its treatment, device problems and bleeding.

Statistical analysis

Continuous data are expressed as mean±standard deviation and normality tests were performed in each variable for determination of whether or not a data set is well-modeled by a normal distribution. The baseline characteristics of the two groups were compared using the two-sample t-test for continuous variables, and chi-square test and Fisher's exact test for categorical variables. Analysis of longitudinal data for the primary endpoint was performed using Kaplan-Meier estimates with the log-rank test. A p-value of <0.05 was considered significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA), version 20.

RESULTS

Patient populations

Among the 164 eligible patients, 72 were assigned to the closure group and 92 to the medical group. Baseline characteristics were similar between the two groups, except age which was higher in the medical group and RoPE scorewhich was higher

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Table 1. Baseline Clinical and Transesophageal Echocardiographic Characteristics

	Closure (n=72)	Medication (n=92)	*p* value
Age, yrs	45.3±9.8	50.2±6.7	0.000
Male, n (%)	53 (73.6)	73 (79.3)	0.457
BMI, mean±SD	24.8±3.0	24.2±3.4	0.239
Hypertension, n (%)	26 (36.1)	30 (32.6)	0.740
Diabetes mellitus, n (%)	7 (9.7)	12 (13.0)	0.626
Dyslipidemia, n (%)	7 (9.7)	11 (12.0)	0.802
Smoker, n (%)	38 (52.8)	58 (63.0)	0.204
Coronary artery disease, n (%)	3 (4.2)	0	0.083
Peripheral arterial obstructive disease, n (%)	0	1 (1.1)	1.000
Chronic obstructive lung disease, n (%)	2 (2.8)	0	0.191
Cerebrovascular events			0.508
Stroke, n (%)	67 (93.1)	88 (95.7)	
TIA, n (%)	5 (6.9)	4 (4.3)	
RoPE score	6.2±1.6	5.7±1.3	0.026
Interatrial right-to-left shunt			0.009
Small, n (%)	13 (18.1)	34 (37.0)	
Moderate to large, n (%)	59 (81.9)	58 (63.0)	
Shunt at rest or septal hypermobility, n (%)	44 (61.1)	22 (23.9)	0.000

BMI, body mass index; TIA, transient ischemic attack; RoPE score, risk of paradoxical embolism score.

Table 2. Medication during Follow-Up Period

	Closure (n=72)	Medication (n=92)	*p* value
Antiplatelet agent	47 (65.3)	78 (84.8)	0.005
Aspirin, n (%)	39 (54.2)	69 (75.0)	0.008
Clopidogrel, n (%)	34 (47.2)	44 (47.8)	1.000
Anticoagulation, n (%)	6 (8.3)	6 (6.5)	0.766
Satin, n (%)	42 (58.3)	69 (75.0)	0.029
ACEI, n (%)	2 (2.8)	5 (5.4)	0.468
ARB, n (%)	26 (36.1)	47 (51.1)	0.060

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. Clinical Outcomes

	Closure (n=72)	Medication (n=92)	*p* value
Primary end point*, n (%)	2 (2.8)	2 (2.2)	1.000
Cerebrovascular events, n (%)	2 (2.8)	1 (1.1)	0.582
Stroke, n (%)	0	1 (1.1)	
TIA, n (%)	2 (2.8)	0	
Death	0	1 (1.1)	1.000
Cardiovascular, n (%)	0	1 (1.1)	
Non-cardiovascular, n (%)	0	0	

TIA, transient ischemic attack.
*Composite of death, nonfatal stroke, TIA, or peripheral embolism.

in the closure group. On TEE, moderate to large right to left shunt were more common in the closure group compared to the medical group (81.9% vs. 63.0%, p=0.009). The presence of shunt at rest or septal hypermobility was also more common in the closure group than in the medical group (61.1% vs. 23.9%, p<0.0001) (Table 1).

Treatments and follow-up

Device implantation was attempted in 72 patients in the closure group and was completed in all patients. In most patients, a 5 Fr multipurpose catheter was passed easily through the PFO, but, in some patients, Swartz™ SL sheath (St. Jude Medical, Plymouth, MN, USA) was necessary for strong back-up support for passage of the guidewire through the PFO. In 12 patients, 18 mm devices were implanted, 25 mm devices in 56 patients, and 30 mm devices in 4 patients. One left atrial wall perforation occurred, but did not require additional management. Therefore, implantation was deemed successful in 71 of the 72 patients (98.6%). Between 1 and 3 months after the index procedure, 55 patients (76.4%) in the closure group underwent TTE or TEE with agitated saline test to confirm the residual shunt after PFO closure. Of these, the device was correctly positioned in all patients (47 with no shunt, 5 with minimal shunt, 1 with moderate shunt, and 2 with severe shunt). Effective closure was defined as closure with no or minimal shunting, and therefore, was achieved in 52 of the 55 patients (94.6%). Among the 92 patients in the medical group, all patients had antiplatelet or anticoagulant treatment at discharge, and none crossed over to the closure group during the follow-up period. From 3 months onward, the use of antiplatelet agent was significantly less frequent in the closure group than in the medical group (p=0.005). Use of oral anticoagulation was rare, but similar in both groups (Table 2). The mean duration of follow-up was 22 months in the closure group and 20 months in the medical group.

Clinical outcomes

Primary end points occurred in 2 patients (2.8%) in the closure group and 2 patients (2.2%) in the medical group (p=1.000) (Ta-

ble 3). Fig. 2 shows the corresponding Kaplan-Meier curves for the primary composite end point. In an analysis of the individual components of the primary end point, TIA occurred in 2 patients (2.0%) in the closure group, and one stroke (1.0%) occurred in the medical group. There was no peripheral embolic event in either group. One patient in the medical group (1.0%) and no patient in the closure group died due to MI at 3 months after enrollment. Otherwise, there was no evidence of device-associated thrombi or new-onset atrial fibrillation in either group. There was also no hospital admission related to PFO or bleeding complications in either group.

DISCUSSION

Main findings

In our study group, PFO closure with the Amplatzer PFO occluder for secondary prevention of stroke or TIA did not result in any difference in the risk of embolic events or death, as compared with medical therapy alone. Other findings of the current study are 1) the recurrence rate of embolic events in our patients was very low; only 1.8% during mean 20-month follow-up period, which is lower compared to other similar studies.[2-4] 2) During the follow-up period, the use of antiplatelet agent was lower in the closure group than in the medical group, which might be a crucial point in an Asian population like ours.

PFO device closure and medical treatment: no definite superiority of one strategy

Based on randomized data, percutaneous PFO closure in patients with ischemic stroke did not appear to be superior to medical therapy.[2-4] These results are consistent with those of our study. Possible reasons include heterogeneous population, insufficient sample size, inappropriate patient selection, low event rate, short follow-up duration, or adverse events eliminating a beneficial effect of PFO closure. On the contrary, meta-analyses, including non-randomized data or focusing on trials which used the Amplatzer closure device, indicate a benefit of PFO closure.[5,6] Furthermore, some studies have shown that the echocardiographic characteristics of PFO in those with high RoPE scores are strongly associated with recurrent stroke or TIA,[10] suggesting that echocardiographic factors seen in high RoPE score patients might provide clues for the PFO-relatedness of the initial stroke in these patients. In our study, higher RoPE score was observed in the closure group. Besides, moderate to large right to left shunt and the shunt at rest or septal hypermobility were more common in the closure group, indicating more benefit obtained from PFO closure. Therefore, its indication should be carefully assessed, and future studies need to focus on optimal patient.

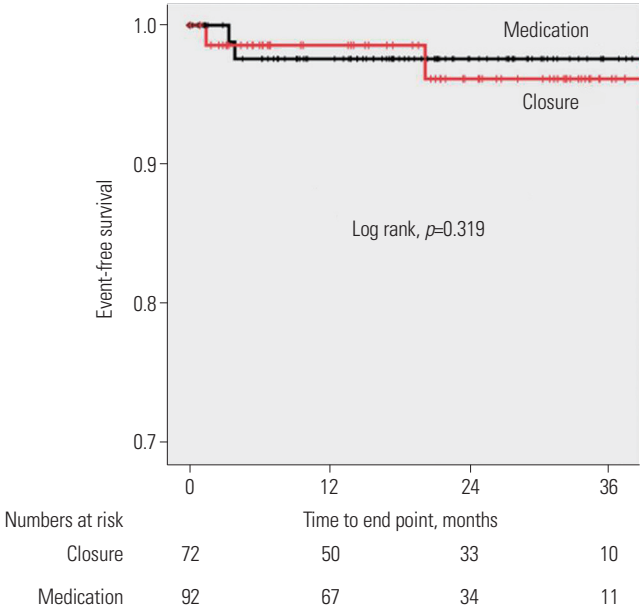

Fig. 2. Kaplan-Meier curves for the primary composite end point.

Consideration for procedure-related problems and hemorrhagic tendency of Asian population on antithrombotic medication

We should also be careful on the fact that the PFO closure procedure is associated with some risks such as bleeding, vascular injury, device embolization, thrombus formation on the device, and tamponade. In most studies, however, the data showed that it can be achieved at a high rate with low complication rates due to the procedure itself.[10-12] In our study, only one procedure-related complication, which did not require additional management, was noted. Also, there was no death or severe complication related to the procedure. This becomes highly relevant as the medical treatment for ischemic stroke or TIA associated with PFO may include dual antiplatelet and/or anticoagulation therapy with their known potential risks. In our study, the use of antiplatelet agent in the closure group was lower than in the medical group, which might be a crucial point in the Asian population, in which hemorrhagic stroke risk (especially with regard to long-term use of antiplatelet or anticoagulation therapy) tends to be higher than in Western populations.[7,13] Currently, there are no studies proving benefit of a specification medication or duration of medication for secondary prevention of ischemic stroke in patients with PFO, and both anti-platelets and/or anticoagulation are considered reasonable options,[9,14-16] pointing that the risk of bleeding would be increased in a time dependent manner with these medications. Given the safe and effective closure observed with the Amplatzer PFO Occluder, as in our study, PFO closure may be a reasonable approach for patients requiring long-term antiplatelet or anticoagulation therapy. However, device-related complications (erosion, migration, thrombosis) during the follow-up period after the procedure as well as residual shunt all play a role in complications or recurrent events.[17,18] Therefore, increasing efforts to optimize device characteristics are necessary.

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Limitations

This study has several limitations as follows. First, this is a non-randomized study with different patient's profile and medications between both groups, and the relatively small sample size and low event rate in a single center study render it difficult to generalize the findings to a larger population. Second, relatively short echocardiographic and clinical follow-up duration in a small population is inadequate for definitive assessment of the absolute risk for recurrent events and bleeding complication of antiplatelet or anticoagulation therapy. Third, selection bias and incomplete follow-up (e.g., shunt grade) make direct comparison of both groups impossible.

Conclusion

Our study comparing PFO closure, using the Amplatzer PFO Occluder and medical therapy alone, in patients with ischemic stroke or recurrent TIA did not show any significant difference in reduction of the risk of recurrent embolic events or death in the real world's setting. However, further investigation of the efficacy and safety of PFO closure is needed in the Asian population, which is prone to bleeding from long-term use of antiplatelet or anticoagulation therapy.

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